

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074182

Trade Name : NAPROXEN TABLETS

Generic Name: Naproxen Tablets 250mg,375mg and 500mg

Sponsor : Sidmak Laboratories, Inc.

Approval Date: June 27, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074182

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Chemistry Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074182

APPROVAL LETTER

ANDA 74-182

JUN 27 1996

Sidmak Laboratories, Inc.
Attention: Arun D. Kulkarni
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Dear Sir:

This is in reference to your abbreviated new drug application dated February 28, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naproxen Tablets USP, 250 mg, 375 mg, and 500 mg.

Reference is also made to your amendments dated August 18, 1992, and May 16, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Naproxen Tablets USP, 250 mg, 375 mg, and 500 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Naprosyn® 250 mg, 375 mg, and 500 mg of Syntex (FP) Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the USP method and its specifications (i.e., NLT (b)4 is dissolved in 45 minutes).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

6/27/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research.

cc: ANDA 74-182
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:

HFD-623/J.Clark/5-31-96
HFD-623/V.Sayeed, Ph.D.
HFD-617/J.Wilson/CSO/6-
HFD-613/C.Park/6-12-96
HFD-613/A.Vezza/6-12-96
X:\NEW\FIRMSNZ\SIDMAK\L
F/T by: bc/6-13-96

/S/

APPROVAL

reviewed 6/25/96

/S/

6/25/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074182

FINAL PRINTED LABELING

NDC 50111-555-01

**Naproxen
Tablets, USP**

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

100 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 250 mg
Dispense in a well-closed container as defined in
the USP.
Store at controlled room temperature 15°-30°C
(59°-86°F).
USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:
Iss. 9/95



SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

NDC 50111-555-02

**Naproxen
Tablets, USP**

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

500 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 250 mg
Dispense in a well-closed container as
defined in the USP.
Store at controlled room temperature
15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:
Iss. 9/95



SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

NDC 50111-555-03

**Naproxen
Tablets, USP**

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

1000 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 250 mg
Dispense in a well-closed container as
defined in the USP.
Store at controlled room temperature
15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:
Iss. 9/95



SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

NDC 50111-557-01

**Naproxen
Tablets, USP**

500 mg

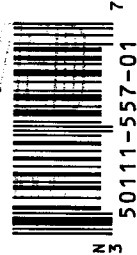
CAUTION: Federal law prohibits
dispensing without prescription.

100 Tablets

Sidmak
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 500 mg
Dispense in a well-closed container as defined in
the USP.
Store at controlled room temperature 15°-30°C
(59°-86°F).
USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:
Iss. 9/95



NDC 50111-557-02

**Naproxen
Tablets, USP**

500 mg

CAUTION: Federal law prohibits
dispensing without prescription.

500 Tablets

Sidmak
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 500 mg
Dispense in a well-closed container as
defined in the USP.
Store at controlled room temperature
15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.



SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
Exp. Date:
Iss. 9/95

NDC 50111-557-03

**Naproxen
Tablets, USP**

500 mg

CAUTION: Federal law prohibits
dispensing without prescription.

1000 Tablets

Sidmak
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 500 mg
Dispense in a well-closed container as
defined in the USP.
Store at controlled room temperature
15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.



SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
Exp. Date:
Iss. 9/95

NDC 50111-556-01

**Naproxen
Tablets, USP**

375 mg

CAUTION: Federal law prohibits
dispensing without prescription.

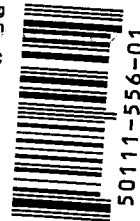
100 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 375 mg
Dispense in a well-closed container as defined in
the USP.
Store at controlled room temperature 15°-30°C
(59°-86°F).
USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:
Iss. 9/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936



50111-556-01

NDC 50111-556-03

**Naproxen
Tablets, USP**

375 mg

CAUTION: Federal law prohibits
dispensing without prescription.

1000 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 375 mg
Dispense in a well-closed container as
defined in the USP.
Store at controlled room temperature
15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.



SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
Exp. Date:
Iss. 9/95

NDC 50111-556-02

**Naproxen
Tablets, USP**

375 mg

CAUTION: Federal law prohibits
dispensing without prescription.

500 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen, USP 375 mg
Dispense in a well-closed container as
defined in the USP.
Store at controlled room temperature
15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.



SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
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ADVERSE REACTIONS: The following adverse reactions are divided into three parts based on frequency and whether or not the possibility exists of a causal relationship between naproxen and one case for each adverse reaction where there is evidence to suggest that there is a causal relationship between drug usage and the reported event.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen (see **CLINICAL PHARMACOLOGY**).

In controlled clinical trials with about 80 children and in well monitored open-label studies with about 400 children with juvenile arthritis, treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in children than in adults.

The following adverse reactions are divided into three parts based on frequency and causal relationship.

Incidence Greater Than 1% (Probable Causal Relationship)

Gastrointestinal: constipation*, heartburn*, abdominal pain*, nausea*, dyspepsia, diarrhea, and stomatitis

Central Nervous System: headache*, dizziness*, drowsiness*, lightheadedness, and vertigo.

Dermatologic: itching (pruritus)*, skin eruptions*, ecchymoses*, sweating, purpura.

Special Senses: tinnitus*, hearing disturbances, visual disturbances.

Cardiovascular: edema*, dyspnea*, palpitations.

General: thirst.

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

Incidence Less Than 1% (Possible Causal Relationship)

The following adverse reactions were reported less frequently than 1% during controlled clinical trials and through voluntary reports since marketing. Those reactions observed through voluntary reporting since marketing are italicized.

Gastrointestinal: Abnormal liver function tests, colitis, gastrointestinal bleeding and/or perforation, hematemesis, jaundice, pancreatitis, melena, vomiting.

Renal: Glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.

Hematologic: Agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia.

Central Nervous System: Depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness.

Dermatologic: Alopecia, photosensitive dermatitis, urticaria, skin rashes, photosensitivity reactions resembling photodermatitis tarda and epidermolysis bullosa.

Special Senses: Hearing impairment.

Cardiovascular: Congestive heart failure.

Respiratory: Eosinophilic pneumonitis.

General: Anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever).

Incidence Less Than 1% (Causal Relationship Unknown)

These observations are being listed to serve as alerting information to the physician.

Hematologic: Aplastic anemia, hemolytic anemia.

Central Nervous System: Aseptic meningitis, cognitive dysfunction.

Dermatologic: Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.

Gastrointestinal: Non-peptic gastrointestinal ulceration, ulcerative stomatitis.

Cardiovascular: Vasculitis.

General: Hyperglycemia, hypoglycemia.

OVERDOSAGE: Significant naproxen overdose may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. A few patients have experienced seizures, but it is not clear whether or not these were drug related. It is not known what dose of the drug would be life threatening. The oral LD₅₀ of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

DOSEAGE AND ADMINISTRATION:

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis: The recommended dose is 250 mg, 375 mg, or 500 mg twice daily. During long-term administration, the dose may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary.

In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk (see **CLINICAL PHARMACOLOGY, Individualization of Dosage**).

Juvenile Arthritis: The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day). Naproxen tablets are not well suited to this dosage so use of naproxen oral suspension is recommended for this indication.

Management of Pain, Primary Dysmenorrhea and Acute Tendinitis and Bursitis: Because the sodium salt of naproxen is more rapidly absorbed, naproxen sodium is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. Naproxen may also be used. The recommended starting dose of naproxen is 500 mg, followed by 500 mg every 12 hours or is 250 mg every 6 to 8 hours as required. The initial total daily dose should not exceed 1250 mg of naproxen. Thereafter, the total daily dose should not exceed 1000 mg of naproxen.

Acute Gout: The recommended starting dose is 750 mg of naproxen, followed by 250 mg every 8 hours until the attack has subsided.

HOW SUPPLIED: Naproxen Tablets, USP:

250 mg - Peach, round, convex, unscored tablets in bottles of 100, 500 and 1000. Debossed SL 555

375 mg - Peach, capsule shaped, unscored tablets in bottles of 100, 500 and 1000. Debossed SL 556

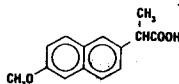
500 mg - Peach, capsule shaped, unscored tablets in bottles of 100, 500 and 1000. Debossed SL 557

Store at controlled room temperature 15° - 30° C (59° - 86° F).

Dispense in a well-closed container as defined in the USP.

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION: Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs. The chemical name for naproxen is (+)-6-Methoxy- α -methyl-2-naphthaleneacetic acid. It has the following structural formula:



MW = 230.26

C₁₇H₁₆O₃

Naproxen is a practically odorless, white to off-white crystalline substance. It is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8.

Each tablet for oral administration contains 250 mg, 375 mg or 500 mg naproxen. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, povidone and FD&C Yellow #6.

CLINICAL PHARMACOLOGY: Naproxen is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Pharmacokinetics: Naproxen itself is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%. The elimination half-life of naproxen ranges from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days and the degree of naproxen accumulation is consistent with this half-life.

Absorption: After administration of naproxen tablets, peak plasma levels are attained in 2 to 4 hours.

Distribution: Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2, and 56.4 mg/L with 500, 1000, and 1500 mg daily doses of naproxen). However, the concentration of unbound naproxen increases proportionally to dose.

Metabolism: Naproxen is extensively metabolized to 6-O-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes.

Elimination: The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%) 6-O-desmethyl naproxen (less than 1%), or their conjugates (66-92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure metabolites may accumulate.

Special Populations:

Children: In children of 5 to 16 years of age with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see **DOSEAGE AND ADMINISTRATION**) were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in children and adults. Pharmacokinetic studies of naproxen were not performed in children of less than 5 years of age.

Renal Insufficiency: Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites, and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency.

Clinical Studies: General Information: Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendinitis and bursitis, and acute gout. Improvement in patients treated for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In a clinical trial comparing standard formulations of naproxen 375 mg BID (750 mg a day) versus 750 mg BID (1500 mg a day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were gastrointestinal events.

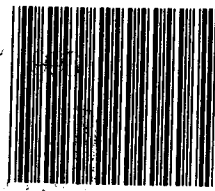
In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in naproxen treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

In patients with acute gout, a favorable response to naproxen was shown by significant clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24 to 48 hours, as well as by relief of pain and tenderness.

Naproxen has been studied in patients with mild to moderate pain secondary to post-operative, orthopedic, post-partum episiotomy, and uterine contraction pain and dysmenorrhea. Onset of pain relief can begin within one hour in patients taking naproxen. Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remedication. The analgesic effect has been found to last for up to 12 hours.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs the combination may result in higher frequency of adverse events than demonstrated for either product alone.



P08-0555

**NAPROXEN
TABLETS, USP**

Iss. 2/96

Manufactured By
SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

P08-0555

Iss. 2/96

In ⁵¹Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of naproxen has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

Individualization of Dosage: Onset of pain relief can begin within one hour in patients taking naproxen.

The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events. A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see **PRECAUTIONS**).

Analgesia/Dysmenorrhea/Bursitis and Tendinitis: Because the sodium salt of naproxen is more rapidly absorbed, naproxen sodium is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. Naproxen may also be used for treatment of acute pain and dysmenorrhea. The recommended starting dose of naproxen is 500 mg followed by 500 mg every 12 hours or 250 mg every 6 to 8 hours, as required. The initial dose should not exceed 1250 mg of naproxen. Thereafter, the total daily dose should not exceed 1000 mg.

Acute Gout: The recommended starting dose is 750 mg of naproxen followed by 250 mg every 8 hours until the attack has subsided.

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis: The recommended dose of naproxen is 250 mg, 375 mg, or 500 mg taken twice daily (morning and evening). During long-term administration the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. In patients who tolerate lower doses well, the dose may be increased to 1500 mg per day when a higher level of anti-inflammatory/analgesic activity is required. When treating patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefit to offset the potential increased risk. The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response (see **CLINICAL PHARMACOLOGY**).

Juvenile Arthritis: The use of naproxen oral suspension allows for more flexible dose titration. In children, doses of 5 mg/kg/day produced plasma levels of naproxen similar to those seen in adults taking 500 mg of naproxen (see **CLINICAL PHARMACOLOGY**).

The recommended total daily dose is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day). (See **DOSEAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE: Naproxen tablets are indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis.

They are also indicated for the treatment of tendinitis, bursitis, acute gout, and for the management of pain and primary dysmenorrhea.

CONTRAINDICATIONS: Naproxen is contraindicated in patients who have had allergic reactions to prescription as well as to over-the-counter products containing naproxen. It is also contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Both types of reactions have the potential of being fatal. Anaphylactoid reactions to naproxen, whether of the true allergic type or the pharmacologic idiosyncratic (e.g., aspirin hypersensitivity syndrome) type, usually but not always occur in patients with a known history of such reactions. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hypotension associated with nonsteroidal anti-inflammatory drugs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date with naproxen have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: NAPROXEN SHOULD NOT BE USED CONCOMITANTLY WITH OTHER NAPROXEN PRODUCTS (SUCH AS NAPROXEN SODIUM) SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.

If the steroid dose is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined periodically.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed non-infectious, non-inflammatory painful conditions.

Because of adverse eye findings in animal studies with drugs of this class it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of naproxen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome associated with naproxen containing products and other NSAIDs since they have been marketed.

A second form of renal toxicity has been seen in patients taking naproxen as well as other nonsteroidal anti-inflammatory drugs. In patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with caution in patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Caution should be used if the drug is given to patients with creatinine clearance of less than 20 mL/minute because accumulation of naproxen metabolites has been seen in such patients.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Hepatic Function: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), naproxen should be discontinued.

Fluid Retention and Edema: Peripheral edema has been observed in some patients receiving naproxen.

Information for Patients: Naproxen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Nonsteroidal Anti-inflammatory Drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS, AND ADVERSE REACTIONS** sections) and likely benefits of naproxen treatment, particularly when it is used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with naproxen.

Laboratory Tests: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients chronically treated with naproxen for signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up and what they should do if certain signs and symptoms do appear (see **WARNINGS, Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy**).

Drug Interactions: The use of NSAIDs in patients who are receiving ACE inhibitors may potentiate renal disease states (see **PRECAUTIONS, Renal Effects**).

In vitro studies have shown that naproxen anion, because of its affinity for protein, may displace from their binding sites other drugs which are also albumin-bound (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Theoretically, the naproxen anion itself could likewise be displaced. Short-term controlled studies failed to show that taking the drug significantly affects prothrombin times when administered to individuals on coumarin-type anticoagulants. Caution is advised nonetheless, since interactions have been seen with other nonsteroidal agents of this class. Similarly, patients receiving the drug and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs (see **CLINICAL PHARMACOLOGY, Clinical Studies: General Information**).

Concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations and peak plasma levels.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported. Naproxen and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Caution should be used if naproxen is administered concomitantly with methotrexate. Naproxen and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

Drug/Laboratory Test Interactions: Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Carcinogenesis: A two-year study was performed in rats to evaluate the carcinogenic potential of naproxen at doses of 8, 16, and 24 mg/kg/day (50, 100, and 150 mg/m²). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m²/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m²/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m²/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naproxen should not be used during pregnancy unless clearly needed.

Non-teratogenic Effects: There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus), use during third trimester should be avoided.

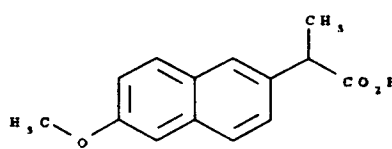
Nursing Mothers: The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies. There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg (as naproxen oral suspension, see **DOSEAGE AND ADMINISTRATION** section) with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074182

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 74-182
3. NAME AND ADDRESS OF APPLICANT
Sidmak Laboratories, Inc.
Attention: Arun D. Kulkarni
17 West Street
P.O. Box 371
East Hanover, NJ 07936
4. BASIS OF SUBMISSION Naprosyn® Tablets; Syntex
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME none
7. NONPROPRIETARY NAME Naproxen Tablets USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
- | | |
|-------------------|--|
| February 28, 1992 | Date of Application |
| July 13, 1992 | CMC/Label NA letter |
| August 4, 1992 | Bio deficiency letter. |
| August 18, 1992 | Bio amendment. |
| November 2, 1992 | Bio review: Acceptable |
| March 2, 1995 | Labeling letter to Sidmak |
| May 3, 1995 | Amendment: CMC and labeling; this review |
| August 10, 1995 | Labeling review: revision needed |
| December 7, 1996 | CMC/label NA letter. |
| May 16, 1996 | CMC/label amendment; this review. |
10. PHARMACOLOGICAL CATEGORY NSAID
11. Rx or OTC Rx 12. RELATED IND/NDA/DMF(s) See sec. 37
13. DOSAGE FORM oral tablet IR 14. POTENCY 250mg, 375mg, 500mg
15. CHEMICAL NAME AND STRUCTURE
Naproxen USP $C_{14}H_{14}O_3$
(+)-6-Methoxy- α -methyl-2-naphthaleneacetic acid.
CAS [22204-53-1]
- 
16. RECORDS AND REPORTS N/A
17. COMMENTS The previous deficiencies are satisfactorily addressed.
18. CONCLUSIONS AND RECOMMENDATIONS Approve; pending labeling.
19. REVIEWER: Jon E. Clark DATE COMPLETED: May 30, 1996
- cc: ANDA 74-182
DUP Jacket
Division File

Endorsements:

HFD-623/J.Clark

HFD-623/V.Sayee

X: NEW FIRMSNZ SIDMAK LTRS&REV 74182AP3.CR

F/T by

/S/

6/11/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074182

BIOEQUIVALENCE REVIEW(S)

NOV 2 1992

Naproxen Tablets
250, 375 and 500 mg
ANDA # 74-182
Reviewer: Moheb H. Makary
WP 74182SDW.892

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
August 18, 1992

Review Of An Amendment Of Bioequivalence Studies And
Waiver Request

I. Background:

The firm has previously submitted an acceptable in vivo bioequivalence studies (under fasting and non-fasting conditions) on its naproxen 500 mg tablet. The studies, however, were found to be incomplete by the Division of Bioequivalence (submission dated February 28, 1992) pending an acceptable in vitro dissolution testing.

In response to the deficiency comment the firm submitted dissolution testing data for all three strengths (250 mg, 375 mg and 500 mg) of the test and reference products, and request for waiver for the in vivo bioequivalence requirements for Sidmak's naproxen tablets 250 mg and 375 mg.

II. Comment:

The firm did not conduct comparative dissolution testing for naproxen 250 mg, 375 mg and 500 mg tablets of the test and reference products at or near the same time. Therefore, the firm was asked to conduct the comparative dissolution testing at the same time (generally within no more than five days).

Reply To Comment:

The firm submitted dissolution testing results for all three strengths of the test and reference products at the same time. The comparative dissolution testing for the test and reference products is acceptable as summarized in Table I. The firm used USP XXII dissolution method which is identical to FDA method:

(b)4
NLT 45 minutes
0.9L 0.1M phosphate buffer, pH 7.4
USP XXII paddle, 50 rpm

The firm's response to the comment is acceptable.

III. Recommendations:

1. The bioequivalence studies (under fasting and non-fasting conditions) conducted by Sidmak Laboratories, Inc., on its

naproxen 500 mg tablet, lot # 91-024T, comparing it to Syntex's Naprosyn^R 500 mg tablet, have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Sidmak's naproxen, 500 mg tablet is bioequivalent to the reference product, Naprosyn^R 500 mg tablet, manufactured by Syntex.

2. The dissolution testing conducted by Sidmak Laboratories, Inc., on its naproxen, 250 mg, 375 mg and 500 mg, lots # 91-022T, 91-023T and 91-024T, respectively, is acceptable. The formulations for the 250 mg and 375 mg strengths are proportionally similar to the 500 mg strength of the test product which underwent bioequivalence testing. waivers of in vivo bioequivalence study requirements for the 250 mg and 375 mg tablets of the test products are granted. The Division of Bioequivalence deems naproxen 250 mg and 375 mg tablets, manufactured by Sidmak Laboratories, Inc., to be bioequivalent to Naprosyn^R, 250 mg and 375 mg, respectively, manufactured by Syntex.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1M phosphate buffer pH 7.4 at 37°C using USP XXII, apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

NLT (b)4 of labeled amount of the drug in the dosage form is dissolved in 45 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of the in vivo bioequivalence and the in vitro dissolution testing and the application is approvable.

The firm should be informed of the above recommendations.

/S/

Moneb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

/S/

ate: 9/30/92

/S/

Concur:

Date: 10/29/92

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

MMakary/9-28-92/wp 74182SDW.892

cc: ANDA # 74-182, original, HFD-630, HFC-130 (J. Allen), HFD-604
(Hare), HFD-658 (Mhatre, Makary), Drug File.

(Please select Typeover for Input.)

Table I. In Vitro Dissolution Testing

Drug (Generic Name): Naproxen Tablets
Dose Strength: 250 mg, 375 mg and 500 mg
ANDA No.: 74-182
Firm: Sidmak Laboratories, Inc.
Submission Date: August 18, 1992
File Name: 74182SDW.892

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of 0.1M phosphate buffer pH 7.4
Specifications: NLT (b)4 in 45 minutes
Reference Drug: Naproxen (Syntex)
Assay Method: (b)4

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 91-022T Strength(mg) 250			Reference Product Lot # 73-144 Strength(mg) 250		
	Mean %	Range	%CV	Mean %	Range	%CV
15	94.92	(b)4 - Confidential Business	2.1	90.03	(b)4 - Confidential Business	4.3
30	101.4	(b)4 - Confidential Business	0.98	99.9	(b)4 - Confidential Business	1.45
45	102.4	(b)4 - Confidential Business	0.9	101.8	(b)4 - Confidential Business	1.7
60	102.3	(b)4 - Confidential Business	0.1	102.1	(b)4 - Confidential Business	1.32
Sampling Times (Minutes)	Test Product Lot # 91-023T Strength(mg) 375			Reference Product Lot # 03411 Strength(mg) 375		
	Mean %	Range	%CV	Mean %	Range	%CV
15	94.66	(b)4 - Confidential Business	1.8	95.3	(b)4 - Confidential Business	1.8
30	98.68	(b)4 - Confidential Business	1.1	99.6	(b)4 - Confidential Business	1.8
45	99.10	(b)4 - Confidential Business	1.4	100.3	(b)4 - Confidential Business	1.7
60	99.43	(b)4 - Confidential Business	1.2	100.55	(b)4 - Confidential Business	1.2

Sampling Times (Minutes)	Test Product Lot # 91-024T Strength(mg) 500			Reference Product Lot # 25030 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.10	(b)4 - onfidenti	2.2	98.20	(b)4 - onfidenti	1.2
30	98.99	Business	1.2	100.82	Business	1.76
45	100.1		0.97	101.59		1.65
60	100.3		0.96	101.69		1.6

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

Naproxen Tablets
250 mg, 375 mg and 500 mg
ANDA # 74-182

AUG 4 1992

Dr. Satish P. Patel
Sidmak Laboratories Inc.
17 West Street
P.O. BOX 371
East Hanover, NJ 07936

Dear Dr. Patel:

Reference is made to the in vivo bioequivalence study, dissolution data and waiver request which you submitted on February 28, 1992 in support of your naproxen tablet.

The material has been reviewed by the Division of Bioequivalence and we have the following comments:

DEFICIENCY COMMENT:

The dissolution testing results for naproxen, 250 mg, 375 mg and 500 mg tablets, lots # 91-022T, 91-023T and 91-024T, respectively, are not acceptable. Dissolution testing for the test products was dated 9/21/91 for the 375 mg tablet and 9/22/91 for the 250 mg and 500 mg tablets. Dissolution testing for the reference products was conducted on 5/13/91 for the 500 mg tablet and on 5/9/91 for the 250 mg and 375 mg tablets. The comparative dissolution testing for the test and reference products should be tested at or near the same time (generally within no more than five days).

RECOMMENDATIONS:

1. From the bioequivalence point of view, the studies are incomplete until acceptable dissolution testing has been submitted for the 500 mg strength.
2. The dissolution testing conducted by Sidmak Laboratories, Inc., on its naproxen, 250 mg and 375 mg tablets, lots # 91-022T and 91-023T, respectively, is not acceptable for the reason cited in the deficiency section. Therefore, waivers of in vivo bioequivalence study requirements for the 250 mg and 375 mg tablets of the test products cannot be granted.

3. The waiver requests should be resubmitted along with the results of the in vitro dissolution testing for the 250 mg and 375 mg tablets.

All responses and correspondence with regard to this letter should be sent to the Office of Generic Drugs, HFD-630.

Sincerely yours,

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: Date _____
HFD-632 Pollock
HFD-650 (Dighe, Greenberg, CST)
stm 07-24-92 (N74182.STD)
bio letter

JUL 16 1992

Naproxen Tablets
250, 375, and 500 mg
ANDA # 74-182
Reviewer: Moheb H. Makary
wp 74182SDW.292

Sidmak Laboratories, Inc.
East Hanover, NJ.
Submission Date:
February 28, 1992

Review Of In Vivo Bioequivalence Studies, Dissolution Data
And Waiver Requests

I. Objective:

The firm has submitted two in vivo bioequivalence studies (under fasting and non-fasting conditions) for its 500 mg naproxen tablet and dissolution data to compare the test product with Syntex's Naprosyn^R 500 mg tablet for approval. The firm has also requested waivers of in vivo bioequivalence study requirements for its naproxen 250 mg and 375 mg tablets. To support the requests, the firm has submitted their in vitro dissolution testing data comparing them with the innovator's respective products, Naprosyn^R 250 and 375 mg tablets.

II. Introduction:

Naproxen is nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Naproxen is fully absorbed when administered orally. Peak concentrations in plasma occur within 2 to 4 hours. The half-life of naproxen in plasma is about 14 hours; this value is increased about twofold in elderly subjects and may necessitate adjustment of dosage. Metabolites of naproxen are almost entirely excreted in the urine. About 30% of the drug undergoes 6-demethylation, and most of this metabolite, as well as naproxen itself, is excreted as the glucuronide or other conjugates. Naproxen is almost completely (99%) bound to plasma protein following normal therapeutic doses. The rate, but not the extent, of absorption is influenced by the presence of food in the stomach.

Naproxen is currently marketed as Naprosyn^R (Syntex) as 250, 375 and 500 mg tablets and as a 125 mg/5 mL suspension.

III. Report # 901413 For Single Dose Fasting Bioequivalence Study

Study site:

(b)4 - Confidential Business

Sponsor:

Sidmak Laboratories, Inc.
East Hanover, NJ.

Investigators:

(b)4 - Confidential Business

Study design:

Randomized, single dose, two-way crossover study under fasting conditions.

Subjects:

Twenty-six healthy male subjects enrolled in the study, all of them completed the crossover. Samples from the first 12 subjects on each sequence to complete the crossover were assayed. Statistical analysis were performed on data from 24 subjects (subjects # 1-24).

Inclusion criteria: The subjects were between 18 and 45 years old and within 15% of their ideal weights (Table of Desirable Weights of Adults, Metropolitan Life Insurance Company, 1983). Each subject received a complete physical examination tests of hematopoietic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study.

Exclusions:

Subjects with history or presence of: cardiovascular, pulmonary, hepatic, renal, hematological or gastrointestinal disease; alcoholism or drug abuse within the last year; any form of bleeding disorders; hypersensitivity or idiosyncratic reaction to naproxen or other nonsteroidal anti-inflammatory drugs were excluded.

Prohibitions:

Subjects were instructed to take no medication (including OTC) for at least 7 days preceding the study. The consumption of alcohol- or xanthine containing products was prohibited for 24 hours prior to dosing in each period and throughout the period of sample collection.

Dose and treatment: All subjects completed an overnight fast (10-hours) before any of the following drug treatments:

Test product: a. One 500 mg naproxen tablet (Silmak), lot # 91-024T, lot size (b)4 -

Reference product: b. One 500 mg Naprosyn tablet (Syntex), lot # 25030, Exp. 2/94.

Food and fluid

intake: Single, oral 500 mg tablet of test or reference product was administered with 240 mL of water. Water was not permitted for 2 hours before and 4 hours after the dose, but was allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after drug administration and at appropriate times thereafter. Meal plans were identical for both periods.

Blood samples: Blood samples (1x5 mL) were collected at 0(pre-dose), 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 60 hours.

Washout period: Fourteen days

Assay Methodology:

Sensitivity:

Recovery:

Specificity:

Precision:

(b)4 - Confidential Business

Stability:

Linearity:

Statistical Analysis:

AUC (finite and infinite), Cmax, Tmax, K_e, and concentrations at each sampling time point were determined. ANOVA was performed at alpha level 0.05 using the GLM procedure of SAS. The 90% confidence intervals (two one-sided tests procedure) were calculated for the parameters AUC(0-t), AUCinf and Cmax. 90% confidence intervals were also calculated for lnAUC(0-t), lnAUCinf and lnCmax.

IV. In Vivo Results:

A total of 26 male subjects enrolled in and completed the study. Samples from the first 12 subjects in each sequence who completed the crossover were analyzed. Thus, statistical analysis were performed on data from 24 subjects (subjects Nos. 1-24). Subject # 16 did not return for the 60-hour blood draw in period 1, and subject # 10 did not return for the 48-hour blood draw in period 2. These data points were set to missing for statistical analysis. Plasma samples for all time points were obtained from all other subjects. A few subjects complained of fatigue, sore throat, headache, pinching sensation in lower back and pain in chest after taking the test or the reference product. No medication was required for any complaint.

The plasma concentrations and pharmacokinetic parameters for naproxen are summarized in Table I and Table II.

Table I

Mean Plasma Concentrations And Pharmacokinetic Parameters
Following An Oral Dose Of 500 mg Naproxen Tablet Under
Fasting Conditions
 (N=24)

<u>Time</u> <u>hr</u>	<u>Sidmak</u>	<u>Syntex</u>
	<u>Test Product</u>	<u>Reference Product</u>
	Lot # 91-024T	Lot # 25030
	ug/mL (CV%)	ug/mL (CV%)
0	0.00 (----)	0.00 (----)
0.33	28.54 (87.7)	24.25 (93.5)
0.66	48.70 (51.1)	42.94 (62.4)
1.00	59.08 (39.2)	49.86 (52.4)
1.50	62.50 (30.5)	51.67 (40.9)
2.00	54.99 (26.7)	54.72 (26.4)
2.50	54.31 (19.6)	55.54 (22.8)
3.00	53.08 (17.3)	53.53 (26.7)
4.00	49.45 (13.0)	47.26 (21.5)
6.00	38.66 (18.1)	39.25 (22.3)
8.00	32.88 (15.1)	33.19 (21.9)
12.00	23.73 (17.1)	24.26 (22.1)
24.00	13.95 (16.1)	13.76 (32.6)

36.00	7.66 (25.1)	7.58 (31.6)
48.00	5.05 (27.6)	5.05 (36.3)
60.00	2.76 (30.3)	3.07 (41.4)

Table II

Pharmacokinetic Parameters*

	<u>Test</u>	<u>Reference</u>	<u>Difference%</u>	<u>90% CI</u>
AUC(0-t) (ug.hr/mL)	951.95	941.98	1.1	96.7-105.5
AUCinf (ug.hr/mL)	1017.78	1017.46	0.00	95.6-104.5
Cmax (ug/mL)	73.86	71.24	3.70	98.4-109.0
Tmax (hr)	1.60	1.92		
Kel (1/hr)	0.046	0.044		
T1/2 (hr)	15.21	15.89		
LNAUC	6.85	6.83		93.4-106.3
LNAUCinf	6.92	6.91		96.6-105.3
LNCmax	4.29	4.25		98.3-109.0

* Based on Least Squares Means.

1. The reviewer noted that the naproxen plasma levels reached a peak at 1.5 hours for the test product and 2.5 hours for the reference product which is in agreement with the literature reported values of 2-4 hours for the reference product (Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th edition, p. 666, 1990). It seems that the test product absorbed faster at early time points compared to the reference product.

2. The percent difference for the mean AUC(0-t) values was 1.1%, whereas for the mean Cmax values it was 3.7%. The AUCinf value for the test product was the same as the AUCinf value for the reference product.

3. As shown in Table II the 90% Confidence intervals for all three parameters are within the acceptable range of 80-120%, and the log-transformed parameters are also within the acceptable range of 80-125%. The reviewer's calculations were similar to those submitted by the firm.

Statistical Evaluation:

1. There were no statistically significant differences between formulations for AUC, AUCinf and Cmax or concentrations at all sampling time points.

2. There were no statistically significant period or sequence effects for any of the above parameters.

V. Report # 901414 For Single Dose Non-fasting Bioequivalence Study:

The objective of the study was to evaluate the effect of food on the bioavailability and bioequivalence of single doses of Sidmak's naproxen 500 mg tablet and Syntex's Naprosyn^R 500 mg tablet.

Study site:

Investigators:

(b)4 - Confidential Business

Study design: A single dose two-way crossover, under non-fasting conditions.

Subjects: 14 healthy male subjects

Inclusion criteria,
Exclusions and

Prohibitions: (Please see report # 901413 for single dose fasting bioequivalence study).

Dose and treatment: Subjects fasted overnight until 20 minutes before dosing when a standard breakfast was served.

Test product: a. 1x500 mg naproxen tablet (Sidmak), lot # 91-024T, lot size (b)4 - (b)4

Reference product: b. 1x500 mg Naprosyn^R tablet (Syntex), lot # 25030, Exp. 2/94.

Food and fluid
intake:

All doses were administered with 240 mL of water following a standard breakfast. Water was not permitted for 2 hours before and 4 hours after the dose, but was allowed at all other times. Standard meals were provided at 4 and 9 hours after drug administration and at appropriate times thereafter. Meals plans were identical for both periods.

Blood samples: Blood samples (1x5 mL) were collected at 0 (pre-dose), 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 60 hours.

Washout period: Fourteen days.

Assay Methodology,

Statistical Analysis: (Please see report # 901413 for single dose

fasting bioequivalence study).

VI. In Vivo Results

Thirteen of the fourteen subjects enrolled in the study completed the crossover. Subject # 5 withdrew for personal reasons approximately 15 hours prior to the dosing in period 2. Samples from the first six subjects in each sequence who completed the crossover were assayed. Thus data from 12 subjects (subject Nos. 1-4, 6-12 and 14) were reported by the firm.

A few subjects complained of dizziness, headache, sore throat, dry throat and fatigue after taking either the test or the reference product. No medication was required for any symptoms.

The plasma concentrations and pharmacokinetic parameters of naproxen are summarized in Table III.

Table III

Mean Plasma Concentrations And Pharmacokinetic Parameters
Following An Oral Dose Of 500 mg Naproxen Tablet
Under Non-fasting Conditions
(N=12)

<u>Time</u> <u>hr</u>	<u>Sidmak</u> <u>Test Product</u> Lot # 91-024T ug/mL (CV%)	<u>Syntex</u> <u>Reference Product</u> Lot # 25030 ug/mL (CV%)
0.00	0.00(0.00)	0.00(0.00)
0.33	7.61(156.80)	7.91(187.20)
0.66	21.28(99.70)	21.81(89.70)
1.00	30.27(67.60)	36.82(56.20)
1.50	41.04(38.70)	45.19(42.70)
2.00	46.94(33.30)	51.36(20.50)
2.50	48.20(30.80)	53.05(15.40)
3.00	50.16(28.00)	52.49(14.40)
4.00	47.22(21.30)	50.23(10.00)
6.00	37.95(19.20)	37.85(9.20)
8.00	31.00(24.30)	29.40(11.20)
12.00	22.90(22.90)	21.86(7.90)
24.00	12.58(17.00)	12.19(12.20)
36.00	6.79(24.80)	6.47(18.90)
48.00	4.33(33.30)	4.08(24.10)
60.00	2.65(32.40)	2.27(42.30)

Pharmacokinetic Parameters

	<u>Test</u>	<u>Reference</u>	<u>T/R</u>
AUC(0-t) (ug.hr/mL)	851.3(14.2)	839.2(8.8)	1.01

AUCinf(ug.hr/mL)	911.3(15.0)	892.2(10.0)	1.02
Cmax(ug/mL)	58.5(14.3)	58.7(13.7)	1.00
Tmax(hr)	2.81	2.39	
Kel(1/hr)	0.046	0.048	
T1/2(hr)	15.25	14.68	

1. The plasma naproxen levels peaked at 2.5 and 3 hours for the reference and test products, respectively, following their administration under non-fasting conditions. The plasma profiles are similar for the test and reference products. The mean Cmax of the test product is the same as the Cmax value of the reference product. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax.

2. The reviewer noted that in the non-fasting study, the mean Cmax and AUC values for the test product decreased by 20.8% and 10.6%, respectively, whereas Tmax increased by 75%, when compared to fasting study. This increase of Tmax in the food study is in agreement with results from the literature.

VII. In Vitro Dissolution Testing

Method: USP XXII apparatus II (paddle) at 50 rpm
Medium: 900 mL of 0.1M phosphate buffer pH 7.4
Number of Tablets: 12
Test Products: Sidmak's naproxen
250 mg tablet, lot # 91-022T
375 mg tablet, lot # 91-023T
500 mg tablet, lot # 91-024T
Reference Products: Syntex's Naprosyn^R
250 mg tablet, lot # 73144
375 mg tablet, lot # 03411
500 mg tablet, lot # 25030

Specification: NLT (b)(4) in 45 minutes

Dissolution testing results are shown in Table IV.

VIII. Formulations:

Sidmak's comparative formulations for its naproxen 250, 375, and 500 mg tablets are shown below.

Naproxen Tablets

Ingredients	250mg mg/Unit	375mg mg/Unit	500mg mg/Unit
Naproxen, USP	250.0	375.0	500.0
Povidone, USP	(b)(4) - Confidential		
Croscamellose Sodium, NF,			

FD&C Yellow #6 AL. Lake
Purified Water, USP (cc)
Magnesium Stearate, NF

(b)4 - Confidential
Business

Total Weight Of The Tablets (mg)	268.0	402.0	536.0
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IX. Deficiency Comment:

The dissolution testing results for naproxen, 250 mg, 375 mg and 500 mg tablets, lots # 91-022T, 91-023T and 91-024T, respectively, are not acceptable. For the test products the firm submitted dissolution testing dated 9/21/91 for the 375 mg tablet and 9/22/91 for the 250 mg and 500 mg tablets. Dissolution testing for the reference products was conducted on 5/13/91 for the 500 mg tablet and on 5/9/91 for the 250 mg and 375 mg tablets. The comparative dissolution testing for the test and reference products should be tested at or near the same time (generally within no more than five days).

X. Comments:

1. The firm's in vivo bioequivalence studies under fasting and non-fasting conditions using 500 mg naproxen tablet are acceptable. The test product is judged to be comparable in both rate and extent of absorption to the reference product. The 90% confidence intervals for all major pharmacokinetic parameters are within the acceptable range of 80-120%. However the study is incomplete due to unacceptable dissolution results indicated in deficiency comment.

2. The in vitro dissolution testing for the test products 250 mg, 375 mg and 500 mg tablets is not acceptable.

3. The formulations for naproxen 250 mg and 375 mg strength are proportionally similar to the 500 mg strength of the test product.

XI. Recommendations:

1. The bioequivalence studies under fasting and non-fasting conditions conducted by Sidmak Laboratories, Inc., on its naproxen, 500 mg tablets, lot # 91-024T, comparing it to Syntex's Naprosyn^R 500 mg tablet, has been found acceptable by the Division of Bioequivalence. The firm however, has not conducted acceptable in vitro dissolution testing as cited in deficiency section. From the bioequivalence point of view, the studies are incomplete.

2. The dissolution testing conducted by Sidmak Laboratories, Inc., on its naproxen, 250 mg and 375 mg tablets, lots # 91-022T and 91-023T, respectively, is not acceptable for reason cited in deficiency section. Therefore, waivers of in vivo bioequivalence study requirements for the 250 mg and 375 mg tablets of the test products cannot be granted.

3. The firm is advised to resubmit the results of in vitro dissolution testing along with the waiver requests for 250 mg and 375 mg tablets.

The firm should be informed of the deficiency comment and recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

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Date: 7/15/92

/S/

Concur:

Date: 7/16/92

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

MMakary/7-14-92/wp 74182SDW.292

cc: ANDA # 74-182, original, HFD-630, HFD-130 (J. Allen), HFD-604 (Hare), HFD-658 (Mhatre, Makary), Drug File.

(Please select Typeover for Input.)

Table IV. in Vitro Dissolution Testing

Drug (Generic Name): Naproxen Tablets
Dose Strength: 250, 375 and 500 mg
ANDA No.: 74-182
Firm: Sidmak Laboratories, Inc.
Submission Date: February 28, 1992
File Name: 74182SDW.292

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 0.1M phosphate buffer pH 7.4 Volume: 900 mL
Specifications: NLT (b)(4) at 45 minutes
Reference Drug: Naproxen (Syntex)
Assay Methodology: (b)(4)

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 91-022T Strength(mg) 250			Reference Product Lot # 73144 Strength(mg) 250		
	Mean %	Range	%CV	Mean %	Range	%CV
15	95.5	(b)(4) - (b)(4)	4.7	101.7	(b)(4) - (b)(4)	2.4
30	102.3	Confidential Business	1.5	103.8	Confidential Business	0.8
45	103.3	Confidential Business	1.3	104.3	Confidential Business	0.8

Sampling Times (Minutes)	Test Product Lot # 91-023T Strength(mg) 375			Reference Product Lot # 03411 Strength(mg) 375		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.2	(b)(4) - (b)(4)	3.2	101.6	(b)(4) - (b)(4)	3.7
30	100.1	Confidential Business	3.2	102.9	Confidential Business	1.6
45	99.8	Confidential Business	1.0	103.1	Confidential Business	1.3

Sampling Times (Minutes)	Test Product Lot # 91-024T Strength(mg) 500			Reference Product Lot # 25030 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	93.6	(b)(4) - (b)(4)	1.6	102.4	(b)(4) - (b)(4)	1.7
30	98.8	Confidential	1.6	103.1	Confidential	1.1
45	99.1	Business	1.4	103.1	Business	1.1

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

Figure 1
Project No. 901413
Mean Plasma Naproxen Concentrations (Under Fasting Condition)
(Semi-Log Plot)

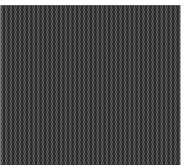
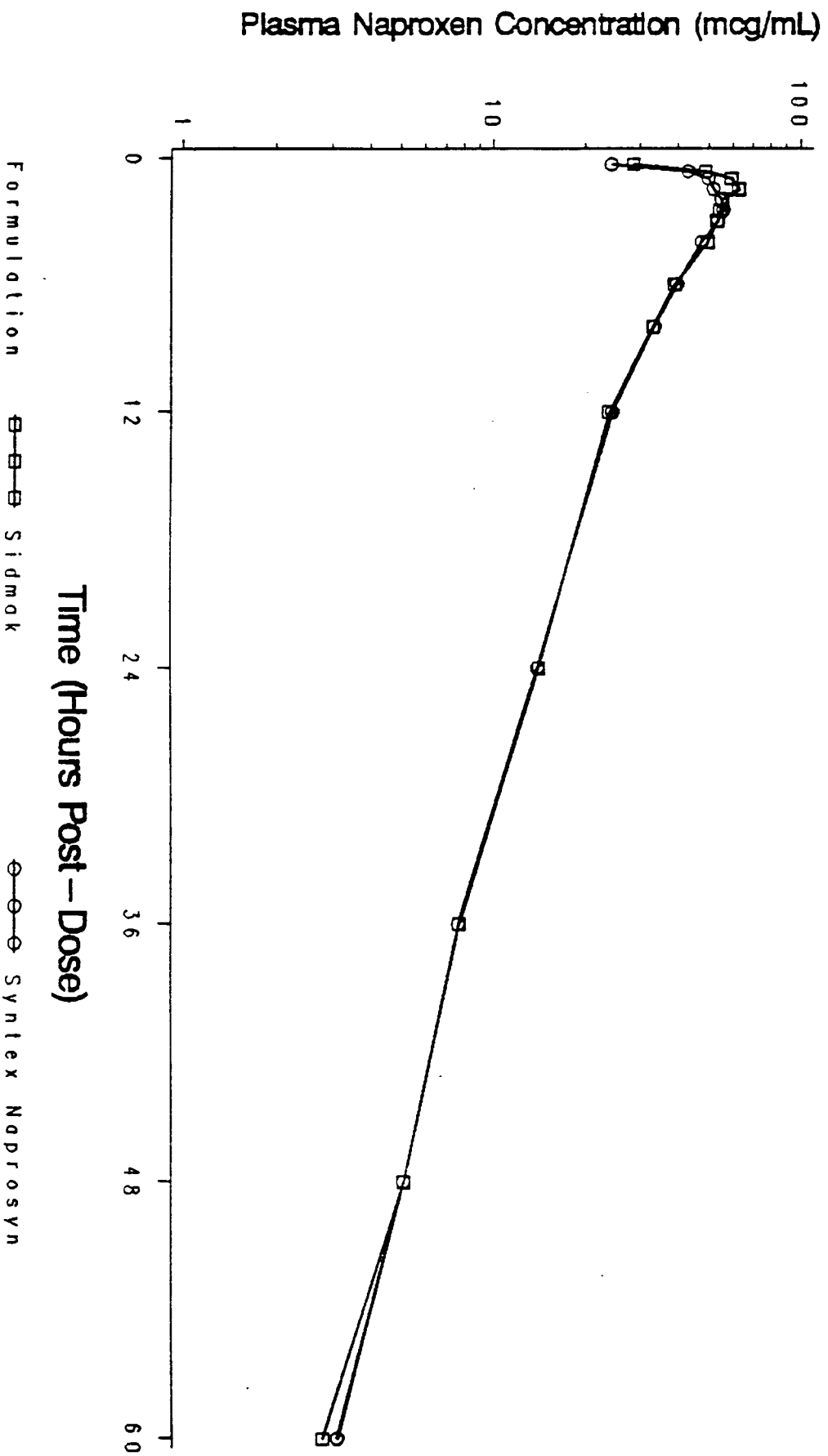


Figure 2
 Project No. 901413
 Mean Plasma Naproxen Concentrations (Under Fasting Condition)
 (Linear Plot)

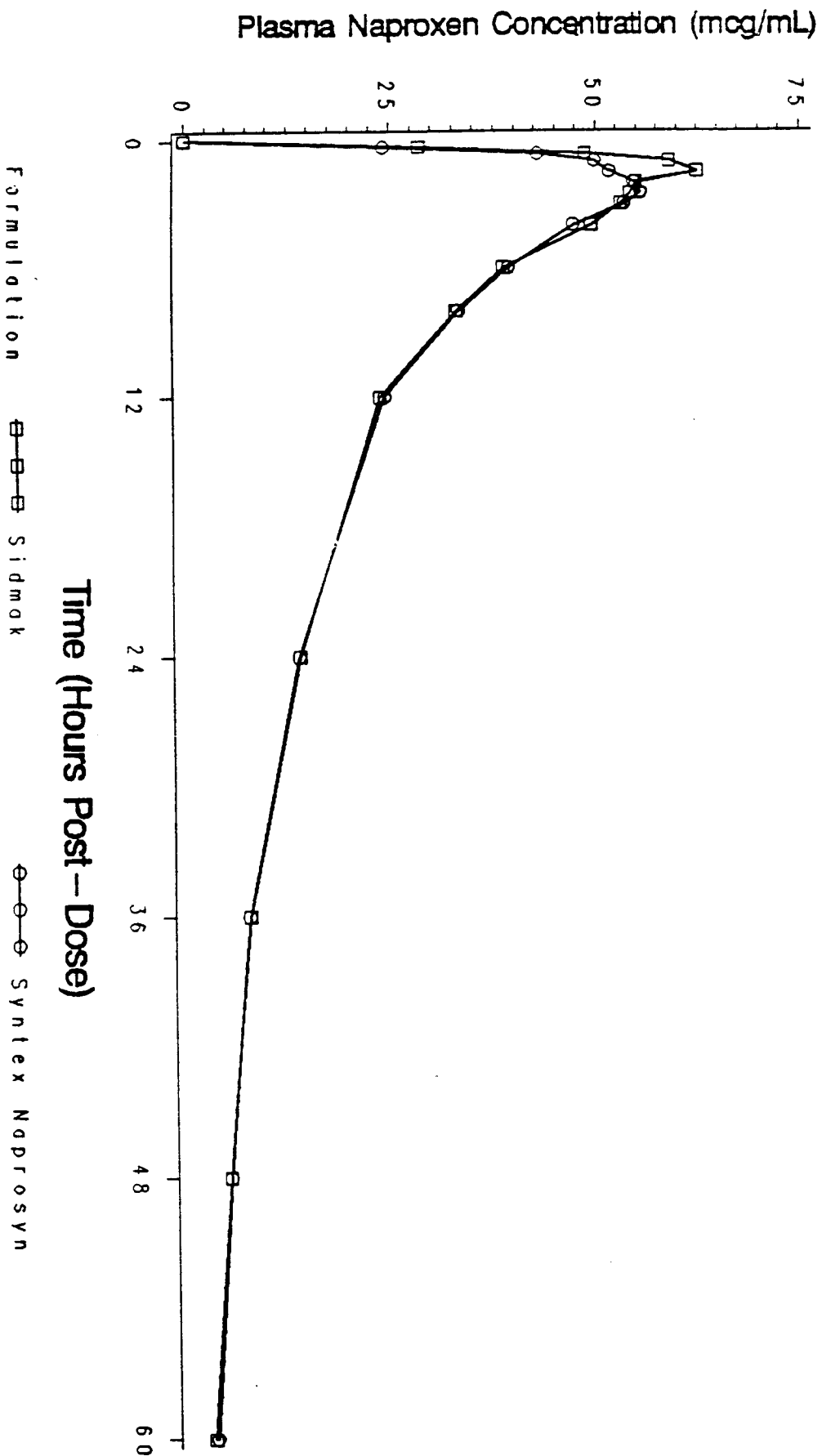


Figure 1
Project No. 901414
Mean Human Plasma Naproxen Concentrations (Under Nonfasting Condition)
(Semi-Log Plot)

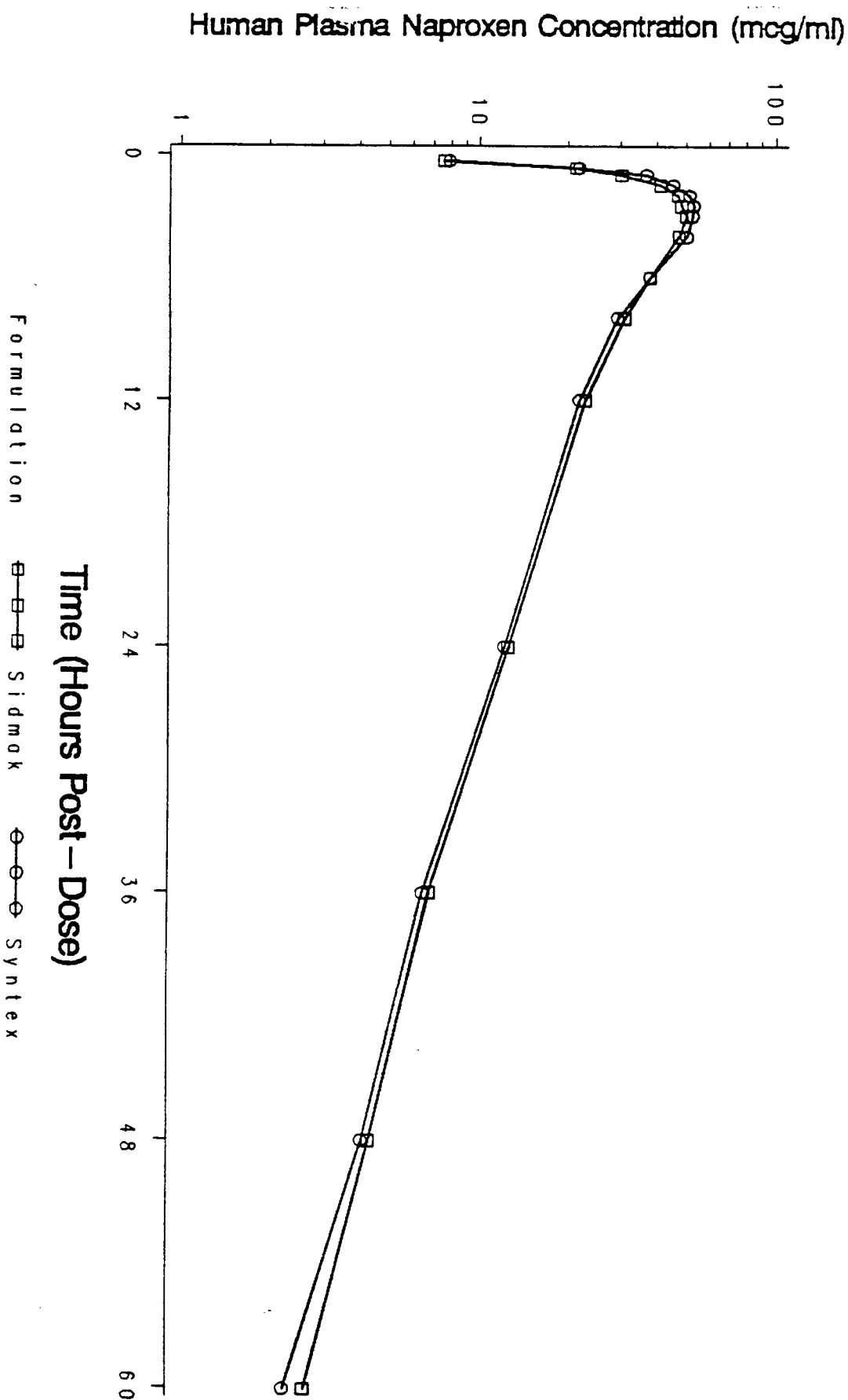


Figure 2
Project No. 901414
Mean Human Plasma Naproxen Concentrations (Under Nonfasting Condition)
(Linear Plot)

